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Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

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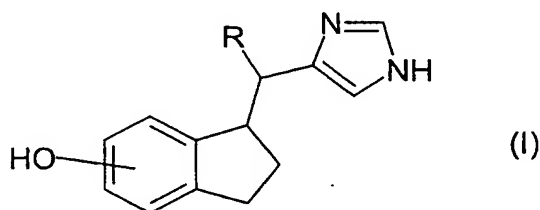
(54) Title: TREATMENT OR PREVENTION OF HYPOTENSION AND SHOCK

(57) Abstract: The present invention relates to a method for the prevention and treatment of hypotension and shock due to low peripheral resistance, comprising administering to a mammal in need thereof an effective amount of a certain imidazole derivative or pharmaceutically acceptable ester or salt thereof. In addition, the present invention relates to a method for the treatment of cardiopulmonary resuscitation, comprising administering to a mammal in need thereof an effective amount of a certain imidazole derivative or pharmaceutically acceptable ester or salt thereof.

TREATMENT OR PREVENTION OF HYPOTENSION AND SHOCK

BACKGROUND OF THE INVENTION

5 The present invention relates to a method for the prevention or treatment of hypotension and shock due to low peripheral resistance. Further, the present invention relates to a method for the treatment of cardiopulmonary resuscitation. Accordingly, the present invention relates to a method for the prevention or treatment of hypotension and shock due to low peripheral resistance by administering an imidazole derivative of the
10 formula I:



wherein R is hydrogen or methyl, or a pharmaceutically acceptable ester or salt thereof.

Further, the present invention relates to a method for the treatment of
15 cardiopulmonary resuscitation by administering an imidazole derivative of formula I or a pharmaceutically acceptable ester or salt thereof.

The present invention also relates to the use of an imidazole derivative of formula I, or a pharmaceutically acceptable ester or salt thereof, in the manufacture of a medicament for the prevention or treatment of hypotension and shock due to low peripheral resistance.
20 Further, the present invention also relates to the use of an imidazole derivative of formula I, or a pharmaceutically acceptable ester or salt thereof, in the manufacture of a medicament for the treatment of cardiopulmonary resuscitation.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be
25 learned by practice of the invention. The objects and advantages of the invention will be

realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the
5 invention, as claimed.

The preparation of the imidazole derivatives of formula I in general has been described in WO 97/12874. Enteral, topical, and parenteral routes of administration and their use as α_2 -adrenoceptor agonists useful in the treatment of hypertension, glaucoma, migraine, diarrhea, ischemia, addiction to chemical substances, anxiety, especially
10 preoperative anxiety, and different neurological, musculoskeletal, psychiatric and cognition disorders as well as a sedative and an analgesic agent, nasal decongestant, and as an adjunct to anaesthesia are discussed in WO 97/12874.

α_2 -Adrenoceptor agonists, such as dexmedetomidine, are known to induce a characteristic pattern of cardiovascular responses including e.g., bradycardia and
15 hypotension and therefore they are typically considered as potential candidates for the treatment of hypertension.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the time-course of mean arterial pressure (MAP) (upper) and heart
20 rate (HR) (lower) in anaesthetized rats after slow intravenous administration (during 5 minutes) of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol at the doses of 1 and 3 $\mu\text{g/kg}$. Means \pm SEM of percent changes from the baseline value are shown, n=6 in each group.

Figure 2 shows the time-course of mean arterial pressure (MAP) (upper) and heart
rate (HR) (lower) in anaesthetized rats after slow intravenous administration (during 5
25 minutes) of dexmedetomidine (DMD) at the doses of 3 and 10 $\mu\text{g/kg}$. Means \pm SEM of percent changes from baseline value are shown, n=6 in each group.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have surprisingly discovered that unlike other pure α_2 -adrenoceptor
30 agonists, the imidazole derivatives of formula I do not decrease the blood pressure after intravenous, intramuscular or subcutaneous administration in a mammal. Accordingly,

they cause an increase in the blood pressure with a reflectory decrease in heart rate after the administration. Thus, the imidazole derivatives of formula I, or a pharmaceutically acceptable ester or salt thereof, can be used in situations where returning the blood from peripheral circulation to the central circulation is needed, like in circulatory shock due to low resistance of peripheral circulation and cardiac arrest. Further, the advantage of the compounds of the present invention compared to adrenalin which is commonly used in these situations, is the lack of direct stimulation of the heart i.e., the heart rate does not raise and cause further ischemia of the heart. Accordingly, an object of the invention is to provide a method for the prevention or treatment of hypotension and shock due to low peripheral resistance by administering an imidazole derivative of formula I, or a pharmaceutically acceptable ester or salt thereof to a mammal. Further, an object of the invention is to provide a method for the treatment of cardiopulmonary resuscitation by administering an imidazole derivative of formula I, or a pharmaceutically acceptable ester or salt thereof to a mammal.

15 The preferred compound of the present invention is 3-(1H-imidazol-4-ylmethyl)-indan-5-ol.

It should be noted that the method for the treatment of hypotension and shock due to low peripheral resistance encompasses all of the potential conditions that require the treatment of hypotension and shock, e.g., hypotension due to vasodilatation, anaphylatic shock, septic shock and post heart surgery shock.

The precise amount of the drug to be administered to a mammal for the prevention and treatment of hypotension and shock due to low peripheral resistance and for the treatment of cardiopulmonary resuscitation is dependent on numerous factors known to one skilled in the art, such as, the compound to be administered, the general condition of the patient, the condition to be treated, the desired duration of use, the type of mammal, the method of administration etc. The desired dose can be administered intravenously, using a bolus dose or by a steady infusion, intramuscularly or subcutaneously. For example, the dose of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol administered intravenously to a human can be from about 10 to 500 μg /patient, preferably about 30-200 μg /patient.

One skilled in the art would recognize the dosage forms suitable in the method of the present invention. The injections or infusions may contain one or more diluents or carriers.

The invention will be further clarified by the following example, which is intended
5 to be purely exemplary of the invention.

EXAMPLE 1

The effects of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol on blood pressure and heart rate after slow intravenous administration were studied in anaesthetized rats.

10 Dexmedetomidine (Orion Corporation Orion Pharma, Finland), a specific α_2 -adrenoceptor agonist was studied as a reference compound.

Male Sprague-Dawley rats (B&K, Sweden), weighing 290-400 g, were anaesthetized with sodium pentobarbital (Mebumat[®] 60 mg/ml) 75 mg/kg i.p.. The left femoral vein was cannulated (PE-50) for slow drug injections. The left femoral artery was cannulated (PE-
15 60) and the mean arterial blood pressure (MAP) and heart rate (HR) were recorded continuously via a Micro MP-15 transducer connected to a Grass Model 7D Polygraph. Arterial pressure was sampled at a rate 150 samples/second and recorded on a Pinus PC computer using the software program AcqKnowledge version 3.5.3 and a MP100A data acquisition unit for analog/digital conversion (BIOPAC Systems, Inc.). Pulse waves of the
20 blood pressure were used for displaying heart rate continuously. The body temperature (rectal) was kept constant at 37 ± 0.5 °C by warming with a lamp above the animal's chest. Only rats with MAP of 73 mmHg or higher were used for the tests. After a stabilizing period of 10-20 min, 3-(1H-imidazol-4-ylmethyl)-indan-5-ol (1 and 3 μ g/kg, as hydrochloride) or dexmedetomidine (3 and 10 μ g/kg, as hydrochlorides) dose was given as
25 slow intravenous injection (during 5 min) by an infusion pump (Perfusor[®] ED 2, B. Braun). The total injection volume was adjusted to 1 ml in each experimental group.

3-(1H-imidazol-4-ylmethyl)-indan-5-ol induced an immediate and dose-dependent increase in MAP (maximally +31 %) and long-lasting decrease in HR (maximally -19%) after slow (during 5 minutes) i.v. dosing of 1 and 3 μ g/kg (see Figure 1 and Table 1).

30 Instead, the reference compound dexmedetomidine (3 and 10 μ g/kg) decreased both MAP and HR (maximally -37% and - 21%, respectively) immediately and dose-dependently (see

Figure 2 and Table 1) after slow intravenous administration at the tested doses.

Table 1.

The effects of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol and dexmedetomidine on mean arterial pressure (MAP) and heart rate (HR) after slow (during 5 minutes) intravenous administration in anaesthetized rats. The values are means \pm SEM, n=6 in each group.

	Dose (μ g/kg)	Time (min)	MPV-2426 AI		Dose (μ g/kg)	Time (min)	Dexmedetomidine	
			MAP(mmHg)	HR (beats/min)			MAP (mmHg)	HR (beats/min)
10	1	0	97 \pm 4	373 \pm 8	3	0	89 \pm 5	348 \pm 12
		3	114 \pm 3	324 \pm 9		3	86 \pm 5	310 \pm 6
		5	112 \pm 3	321 \pm 9		5	79 \pm 7	310 \pm 5
		10	83 \pm 4	327 \pm 7		10	61 \pm 4	308 \pm 4
15		20	84 \pm 4	319 \pm 9		20	65 \pm 2	309 \pm 5
		30	80 \pm 3	317 \pm 9		30	67 \pm 2	309 \pm 5
20	3	0	94 \pm 5	366 \pm 11	10	0	92 \pm 2	383 \pm 11
		3	123 \pm 9	309 \pm 7		2	94 \pm 4	308 \pm 5
		5	117 \pm 12	311 \pm 4		5	75 \pm 6	309 \pm 3
		10	88 \pm 4	321 \pm 4		10	59 \pm 3	303 \pm 3
		20	83 \pm 5	321 \pm 6		20	68 \pm 2	296 \pm 7
		30	77 \pm 3	305 \pm 6		30	73 \pm 2	297 \pm 6

25

Immediate and dose-dependent initial hypertensive action was seen after administration of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol at all tested doses. In addition, immediate, and long-lasting bradycardic action was noted after administration 3-(1H-imidazol-4-ylmethyl)-indan-5-ol at all tested doses. Instead, the reference compound dexmedetomidine (3 and 10 μ g/kg) decreased both MAP and HR after slow intravenous administration. After slow intravenous administration 3-(1H-imidazol-4-ylmethyl)-indan-5-ol produces both hypertensive and bradycardic actions, unlike dexmedetomidine, which in turn has typical cardiovascular effects of an alpha-2-adrenoceptor agonist.

Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is

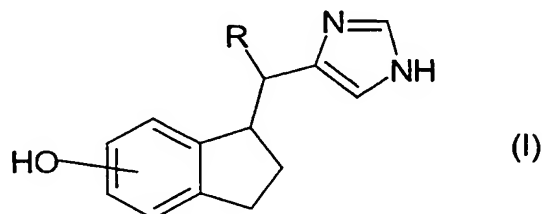
intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The references discussed herein are specifically incorporated by reference in their entirety.

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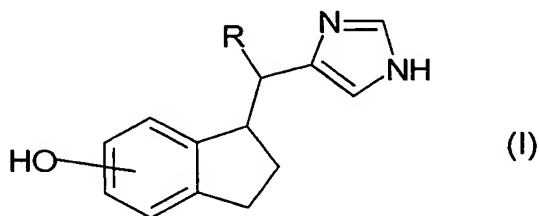
CLAIMS:

1. A method for the prevention or treatment of hypotension and shock due to low peripheral resistance, comprising administering to a mammal in need thereof an effective
 5 amount of an imidazole derivative of formula I:



wherein R is hydrogen or methyl, or a pharmaceutically acceptable ester or salt thereof.

- 10 2. A method for the treatment of cardiopulmonary resuscitation, comprising administering to a mammal in need thereof an effective amount of an imidazole derivative of formula I



wherein R is hydrogen or methyl, or pharmaceutically acceptable ester or salt thereof.

15

3. The method according to any one of claims 1-2, wherein 3-(1H-imidazol-4-ylmethyl)-indan-5-ol is administered.
4. The method according to claim 3, wherein 3-(1H-imidazol-4-ylmethyl)-indan-5-ol
 20 hydrochloride is administered.

5. The method according to any one of claims 1-4, wherein the administration is intravenous.

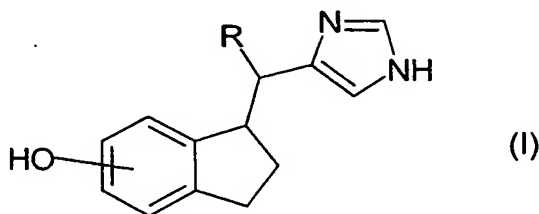
6. The method according to any one of claims 1-5, wherein the mammal is a human.

5

7. The method according to any one of claims 5-6, wherein the effective amount administered is from about 10 – 500 μg /patient.

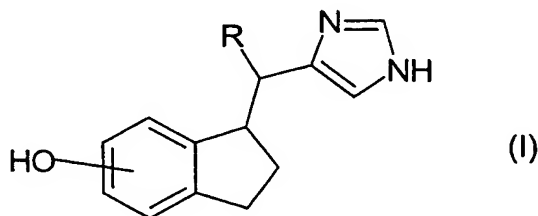
8. The method according to claim 7, wherein the effective amount administered is from about 30 -200 μg /patient.

9. Use of an imidazole derivative of formula I:



wherein R is hydrogen or methyl, or a pharmaceutically acceptable ester or salt thereof, in the manufacture of a medicament for the prevention or treatment of hypotension and shock due to low peripheral resistance.

10. Use of an imidazole derivative of formula I:



20 wherein R is hydrogen or methyl, or a pharmaceutically acceptable ester or salt thereof, in the manufacture of a medicament for the treatment of cardiopulmonary resuscitation.

11. Use according to any one of claims 9-10, wherein the drug is 3-(1H-imidazol-4-ylmethyl)-indan-5-ol.

5 12. Use according to claim 11, wherein the drug is 3-(1H-imidazol-4-ylmethyl)-indan-5-ol hydrochloride.

13. Use according to any one of claims 9-11, wherein the drug is administered intravenously to a human in an amount of from about 10 to 500 μg /patient.

10

14. The method according to claim 13, wherein the drug is administered in an amount of from about 30 to 200 μg /patient.

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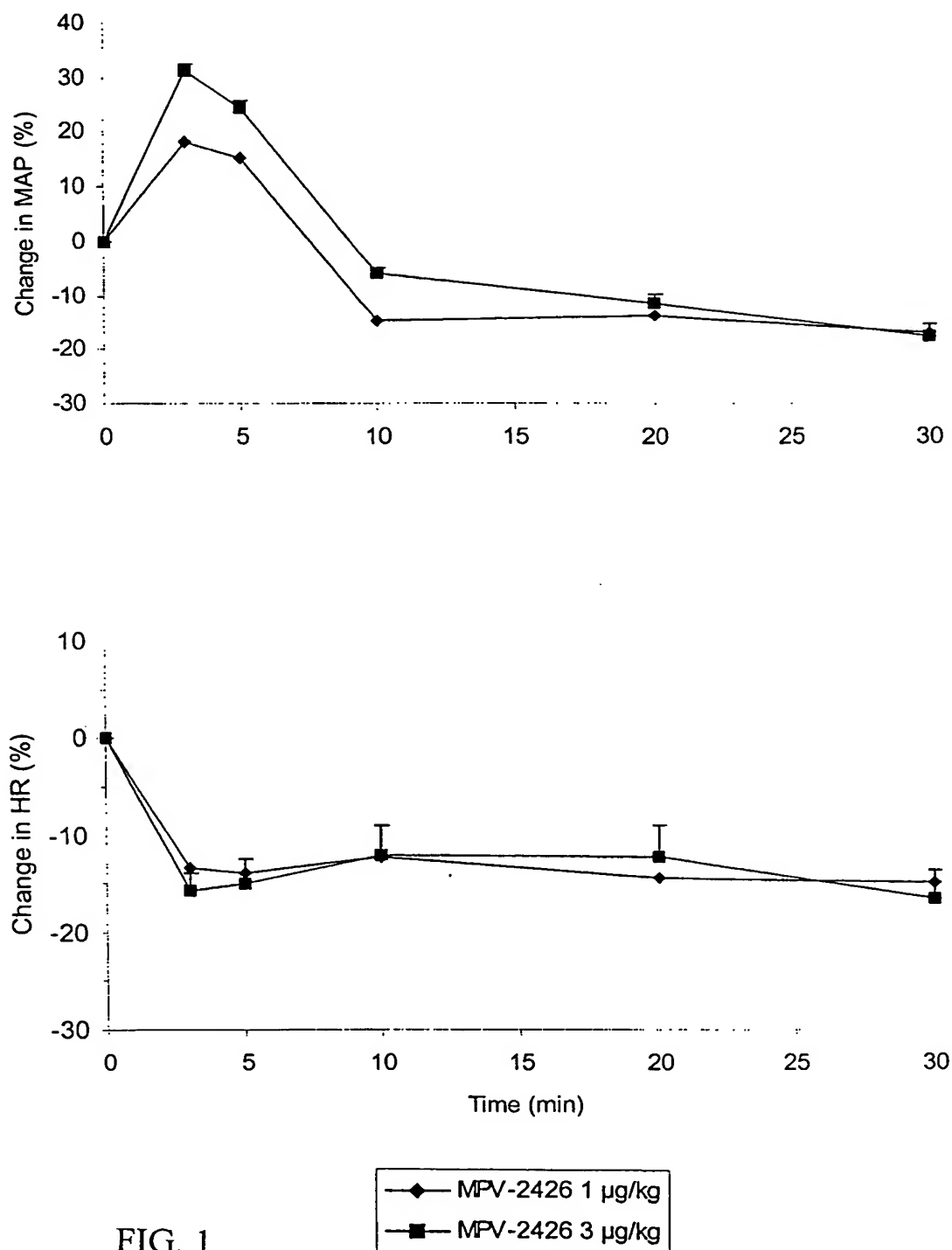
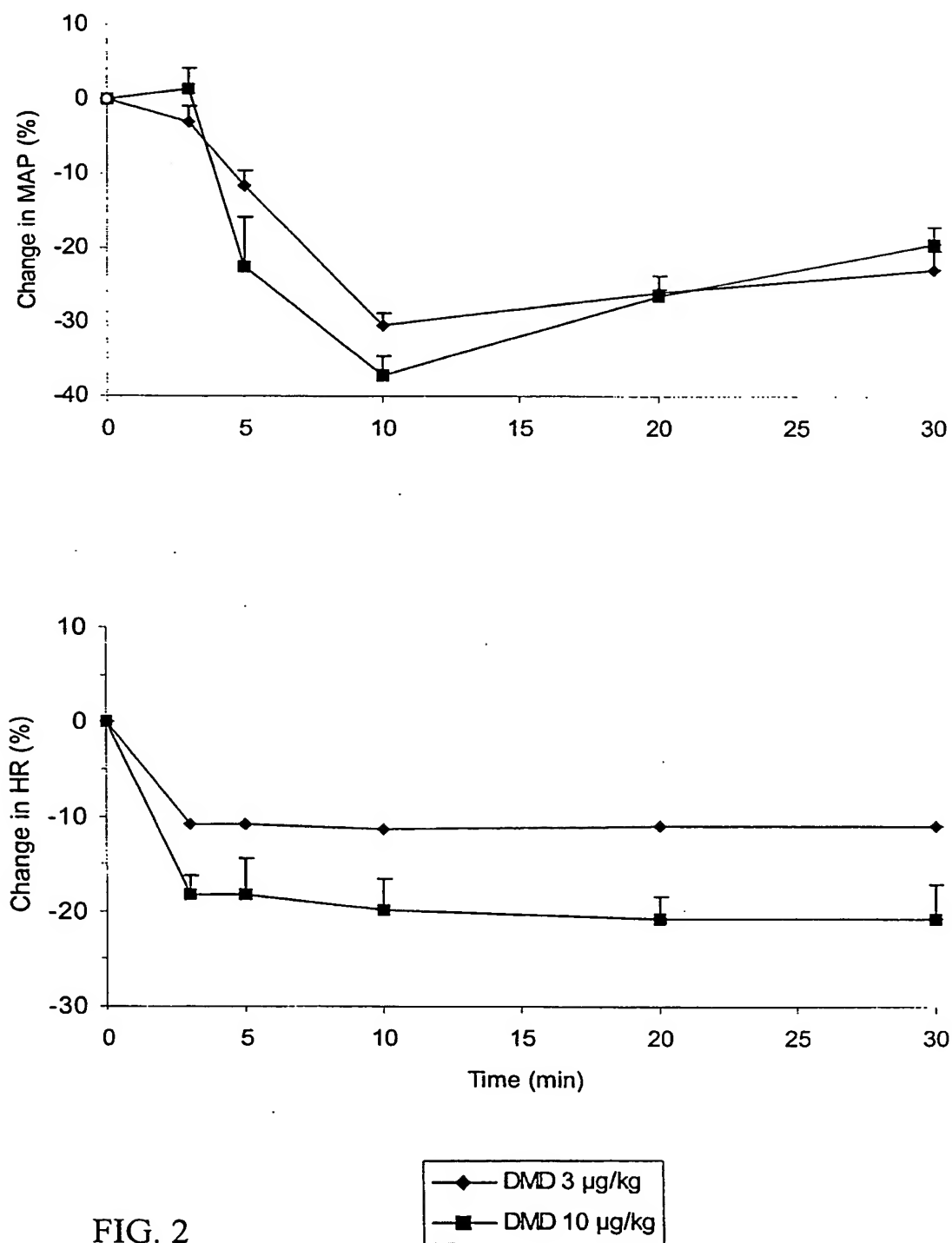


FIG. 1

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 00/00935

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/4174, A61P 9/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CAPLUS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Anesthesiology, Volume 91, No 5, November 1999, James C. Eisenach, M.D. et al, "Antinociceptive and Hemodynamic Effects of a Novel alpha-2-Adrenergic Agonist, MPV-2426, in Sheep" page 1425 - page 1436 --	1-14
A	WO 9712874 A1 (ORIONYHTYMÄ OY), 10 April 1997 (10.04.97) -- -----	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

23 January 2001

Date of mailing of the international search report

26.02.2001

Name and mailing address of the International Searching Authority
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Authorized officer

EVA JOHANSSON/EÖ
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00935

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1-8**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 00/00935

Claims 1-8 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Form PCT/ISA/210 (extra sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 00/00935

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9712874	A1	10/04/97	AU	708002 B	29/07/99
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				BG	102324 A	29/01/99
				CA	2231535 A	10/04/97
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				GB	9520150 D	00/00/00
				HU	9802927 A	28/10/99
				IL	123721 D	00/00/00
				JP	2000507914 T	27/06/00
				LT	4460 B	25/02/99
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				LV	12108 A,B	20/08/98
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				SK	43998 A	07/10/98

Form PCT/ISA/210 (patent family annex) (July 1998)

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